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G_{olf} and G_s in Rat Basal Ganglia: Possible Involvement of G_{olf} in the Coupling of Dopamine D_1 Receptor with Adenylyl Cyclase

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Using specific antibodies and cDNA probes, we have investigated, in rat basal ganglia, the distribution and the regulation of the expression of the α subunits of G_s and G_{olf}, two GTP-binding proteins (G-proteins) that stimulate adenylyl cyclase. We confirmed that $G_{olf}\alpha$ is highly expressed in caudate-putamen, nucleus accumbens, and olfactory tubercle, whereas $G_s\alpha$ is less abundant in these areas than in the other brain regions. Intrastriatal injections of quinolinic acid decreased dramatically the levels of $G_{olf}\alpha$ protein in the striatum and the substantia nigra, and those of $G_{olf}\alpha$ mRNA in the striatum. Retrograde lesions of striatonigral neurons with volkensin reduced markedly the levels of D_1 dopamine (DA) binding sites, as well as those of $G_{olf}\alpha$ protein and mRNA in the striatum, without altering D_2 binding sites. In contrast, both types of lesions increased the levels of $G_s\alpha$ protein in the striatum and substantia nigra. Immunocytochemistry showed the presence of $G_{olf}\alpha$ protein in striatal medium-sized neurons and in several other neuronal populations. These results demonstrate that striatonigral neurons contain high levels of $G_{olf}\alpha$ and little, if any, $G_s\alpha$, suggesting that the coupling of D_1 receptor to adenylyl cyclase is provided by $G_{olf}\alpha$. The levels of $G_{olf}\alpha$ were five- to sixfold higher in the striatum than in the substantia nigra, indicating a preferential localization of $G_{olf}\alpha$ in the somatodendritic region of striatonigral neurons and providing a basis for the low efficiency of D_1 receptor coupling in the substantia nigra. Six weeks after 6-hydroxydopamine lesions of DA neurons, an increase in $G_{olf}\alpha$ (+53%) and $G_s\alpha$ (+64%) proteins was observed in the striatum. This increase in $G_{olf}\alpha$ levels may account for the DA-activated adenylyl cyclase supersensitivity, without change in D_1 receptors density, that follows destruction of DA neurons. Fine regulation of the levels of $G_{olf}\alpha$ in physiological or pathological situations may be a critical parameter for the efficiency of DA neurotransmission.

Key words: G-protein, $G_{olf}\alpha$, $G_s\alpha$, D_1 receptor, striatum, substantia nigra, basal ganglia, dopamine, signal transduction, adenylyl cyclase, receptor supersensitivity

Receptors with seven putative transmembrane domains are known to stimulate adenylyl cyclase via two homologous heterotrimeric G-proteins, G_s and G_{olf}, composed of α, β, and γ subunits and differing by their α subunits (Simon et al., 1991). Whereas G_s is found in numerous cell types (Gilman, 1987), G_{olf} is thought to mediate specifically the stimulation of type III adenylyl cyclase by odorant signal receptors in the olfactory neuroepithelium (Jones and Reed, 1989; Bakalyar and Reed, 1990; Menco et al., 1992). However, the recent demonstration of the presence of $G_{olf}\alpha$ mRNA in rat basal ganglia (Drinnan et al., 1991) suggests its possible involvement in the signal transduction cascade initiated by neurotransmitter-triggered receptors. One of the aims of the present study was to substantiate this possibility by studying the localization of $G_{olf}\alpha$ in striatonigral neurons, which express high levels of dopamine (DA) D_1 receptors (Gerfen et al., 1990; Harrison et al., 1990; Le Moine et al., 1991; Sibley and Monsma, 1992). OK.

Several lines of evidence suggest that the coupling efficiency of D_1 receptors with adenylyl cyclase could be a factor regulating the function of these receptors. In rat striatum, experiments with an irreversible D_1 blocker, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, have shown that 40% of D_1 receptors are "spare" receptors, not coupled to adenylyl cyclase, and have suggested that coupling could represent a limiting step in the D_1 receptor–dependent activation of adenylyl cyclase (Hess et al., 1987). Accordingly, long-lasting interruption of DA neurotransmission may increase the coupling efficiency of D_1 receptors in the striatum, since lesions of nigrostriatal DA neurons or chronic treatment with reserpine increases DA-stimulated adenylyl cyclase without changing the D_1 receptor density (Savasta et al., 1988; Hervé et al., 1989; Missale et al., 1989; Cowburn et al., 1991). The comparison of D_1 receptor densities and DA-sensitive adenylyl cyclase activities in several cerebral regions suggests also the existence of a regional variability in the coupling efficiency between these two proteins (Andersen et al., 1990). For instance, the DA-stimulated adenylyl cyclase activity is sevenfold higher in the striatum than in the substantia nigra, whereas the density of D_1 receptors labeled by ^{3}H-SCH23390 is similar in both structures (Hervé et al., 1992). Moreover, the density of D_1 receptors in high-affinity state for agonists, which is thought to correspond to the form associated with the G-protein (DeLean et al., 1980; Leff and Creese, 1985), is much lower in the substantia nigra than in the striatum (Hervé et al., 1992). These observations could be explained by variations in the levels of stimulatory G-proteins, which would be lower in the substantia nigra than in the striatum, and which would increase following long-lasting interruption of DA neurotransmission. In the present study, using cDNA and antibody probes specific for $G_s\alpha$ and $G_{olf}\alpha$, we demonstrate that $G_{olf}\alpha$ is enriched in striatonigral neurons, contrasting with $G_s\alpha$, which does not seem to be expressed in these neurons. We also show that $G_{olf}\alpha$ levels are

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